

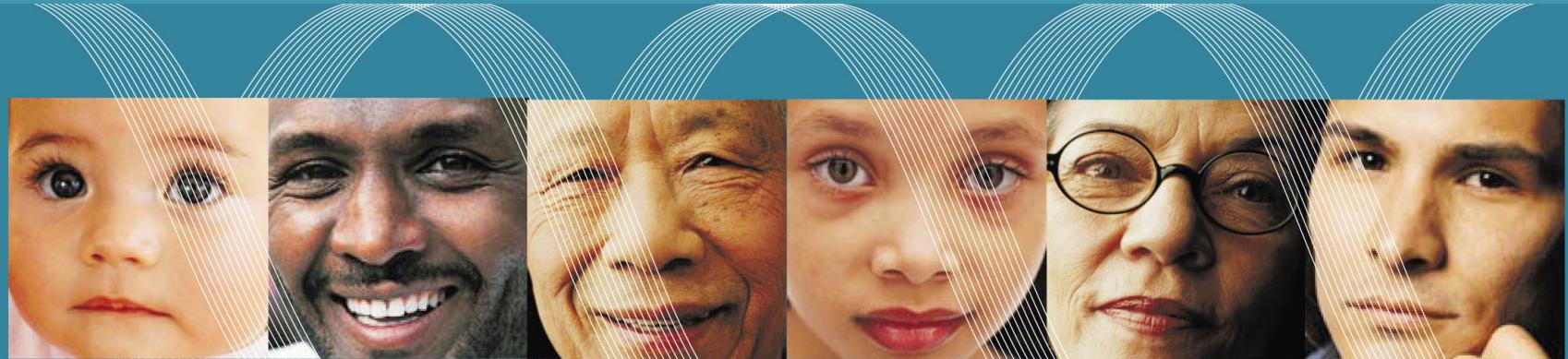
Demystifying Medicine, January 6, 2015
Attention Deficit Hyperactivity Disorder (ADHD)
From Causes To Treatment and Long-Term Outcome



Attention Deficit Hyperactivity Disorder (ADHD): From Causes To Treatment

Max Muenke, M.D.
Chief, Medical Genetics Branch
Director, Medical Genetics and Genomic Medicine Training
National Human Genome Research Institute
National Institutes of Health

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No Conflict

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Outline

- Introduction
- Genetics of ADHD
- Genetic Approaches to Understanding ADHD
- ADHD Susceptibility Genes: *LPHN3* & *NCAM1*
- Pharmacogenetic Studies in ADHD
- *LPHN3* in Animal Studies
- Conclusion

Attention Deficit Hyperactivity Disorder (ADHD)

- Excessive inattention, hyperactivity and impulsivity for a given developmental level
Multi-point DSM-V criteria for each category

Most common behavioral disorder of childhood

Prevalence: 7-11% of children ages 6-12

- Associated DSM-V disorders
 - ODD - Oppositional Defiant Disorder
 - CD - Conduct Disorder
 - SUD – Substance Use Disorder
- Evidence for genetic basis of ADHD
 - Familial ADHD
 - Twin and adoption studies

ADHD: Inattention

Often

- careless errors, inattentive to detail
- sustains attention poorly
- *appears* to not be listening
- follows through poorly on obligations
- disorganized
- avoids or dislikes sustained mental effort
- loses needed objects
- easily distracted
- forgetful

ADHD: Hyperactivity/ Impulsivity

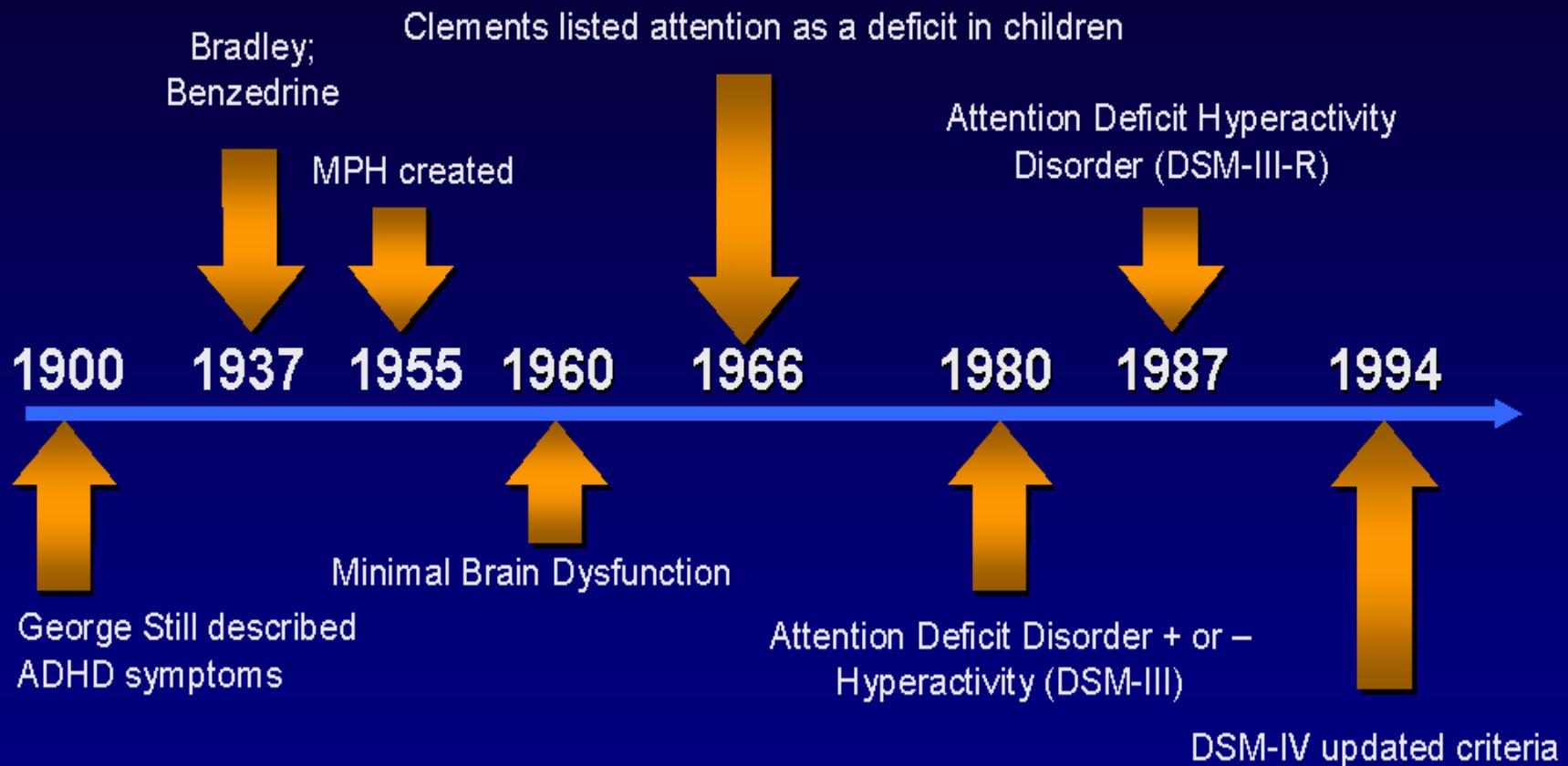
Often

- fidgets or squirms
- can't stay seated
- restless (subjective in adolescents)
- loud, noisy
- always “on the go”
- talks excessively
- blurts out
- impatient
- intrusive

DSM-V Diagnosis of ADHD

- 6/9 symptoms required for each subtype
- Clear impairment (social, academic, or occupational)
- Some symptoms cause impairment by age 12
- Impairment present in more than one setting
- Not accounted by another condition (e.g. autism, psychosis, depression, ...)

ADHD Historical Timeline



Bradley (1937) — original conceptualization of ADHD involved testing of response to stimulant.

History

- Hippocrates: 493 BCE “patients with quickened responses to sensory experience, but also less tenaciousness because the soul moves on quickly to the next impression. Proposed etiology “overbalance of fire over water”. Treatment included: “barley rather than wheat bread, fish rather than meat, water drinks and many natural and diverse physical activities”.
- In 1845 Dr. Heinrich Hoffmann a German Pediatrician wrote a book for children with illustrations, about children and inappropriate behaviors



Slovenly Peter or Cheerful Stories and Funny Pictures for Good Little Folks

Dr. Heinrich Hoffmann

translated into English jingles by

Mark Twain

Die Geschichte vom Zappel-Philipp



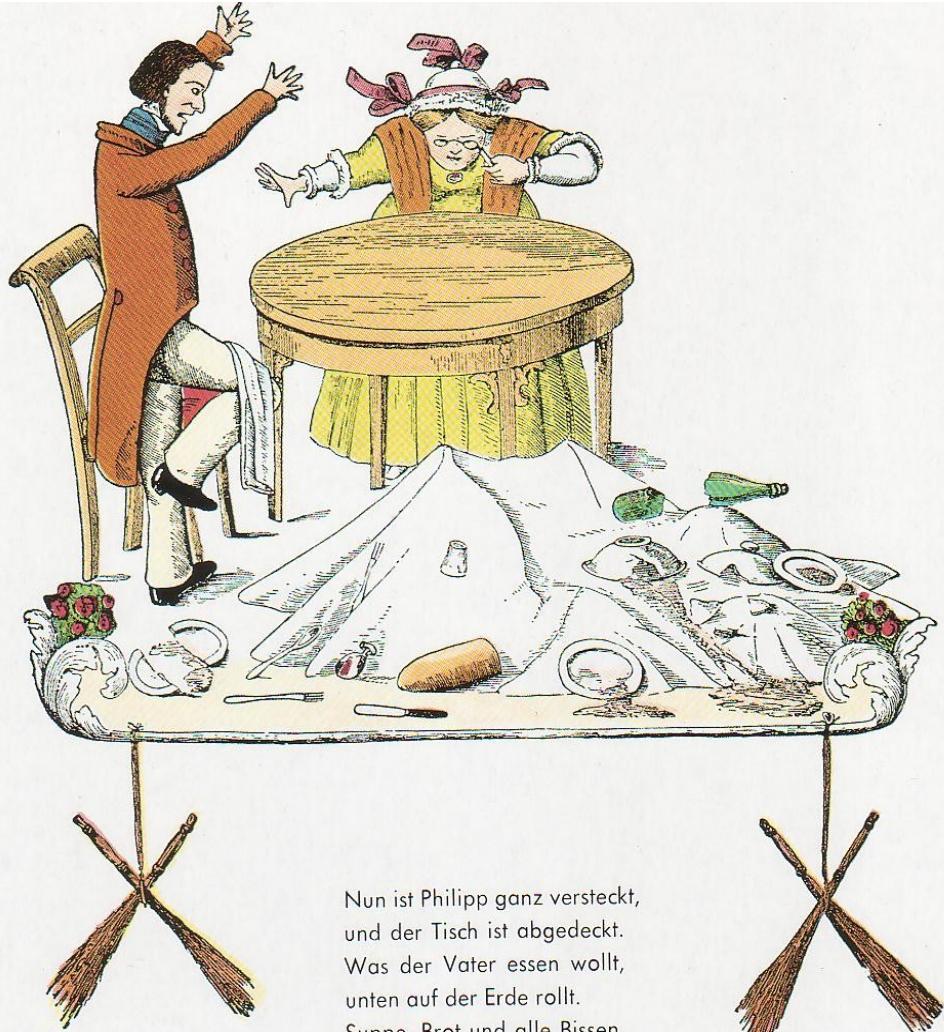
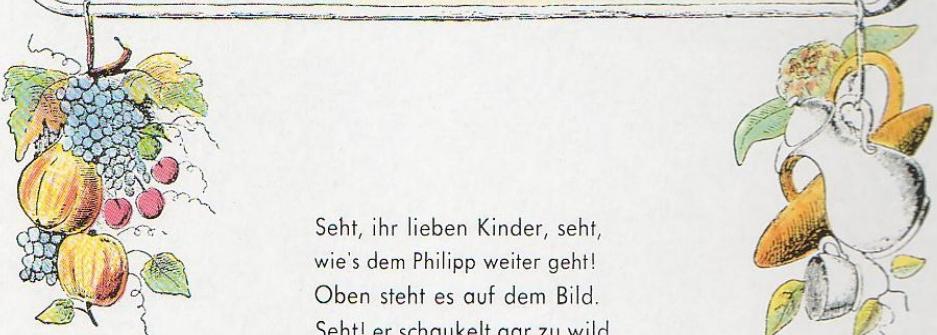
»Ob der Philipp heute still
wohl bei Tische sitzen will?«
Also sprach in ernstem Ton
der Papa zu seinem Sohn,
und die Mutter blickte stumm
auf dem ganzen Tisch herum.
Doch der Philipp hörte nicht,
was zu ihm der Vater spricht.
Er gaukelt
und schaukelt,
er trappelt
und zappelt
auf dem Stuhle hin und her.
»Philipp, das mißfällt mir sehr!«

The Story of Fidgety Philip

“Let me see if Philip can
Be a little gentleman;
Let me see if he is able
To sit still for once at table.”
Thus spoke, in earnest tone,
The father to his son;
And the mother looked very grave
To see Philip so misbehave.



Seht, ihr lieben Kinder, seht,
wie's dem Philipp weiter geht!
Oben steht es auf dem Bild.
Seht! er schaukelt gar zu wild,
bis der Stuhl nach hinten fällt.
Da ist nichts mehr, was ihn hält.
Nach dem Tischtuch greift er, schreit.
Doch was hilft's? Zu gleicher Zeit
fallen Teller, Flasch und Brot.
Vater ist in großer Not,
und die Mutter blicket stumm
auf dem ganzen Tisch herum.



Nun ist Philipp ganz versteckt,
und der Tisch ist abgedeckt.
Was der Vater essen wollt,
unter auf der Erde rollt.
Suppe, Brot und alle Bissen,
alles ist herabgerissen.
Suppenschüssel ist entzwei,
und die Eltern stehn dabei.
Beide sind gar zornig sehr,
haben nichts zu essen mehr.



Die Geschichte vom Hanns Guck-in-die-Luft



Wenn der Hanns zur Schule ging,
stets sein Blick am Himmel hing.
Nach den Dächern, Wolken, Schwalben
schaut er aufwärts allenthalben.
Vor die eignen Füße dicht,
ja, da sah der Bursche nicht,
also daß ein jeder ruft:
»Seht den Hanns Guck-in-die-Luft!«

Kam ein Hund daher gerannt;
Hännlein blickte unverwandt
in die Luft.
Niemand ruft:
»Hanns! gib acht, der Hund ist nah!«
Was geschah?
Bauz! perdauz! – da liegen zwei,
Hund und Hännchen nebenbei.

The Story of Johnny Head-in-Air

As he trudged along to school,
It was always Johnny's rule
To be looking at the sky
And the clouds that floated by;
But what just before him lay,
In his way,
Johnny never thought about;
So that every one cried out -
“Look at little Johnny there,
Little Johnny Head-In-Air!”



Einst ging er an Ufers Rand
mit der Mappe in der Hand.
Nach dem blauen Himmel hoch
sah er, wo die Schwalbe flog,
also daß er kerzengrad
immer mehr zum Flusse trat.

Und die Fischlein in der Reih
sind erstaunt sehr, alle drei.

Doch zum Glück da kommen zwei
Männer aus der Näh herbei,
und die haben ihn mit Stangen
aus dem Wasser aufgefangen.

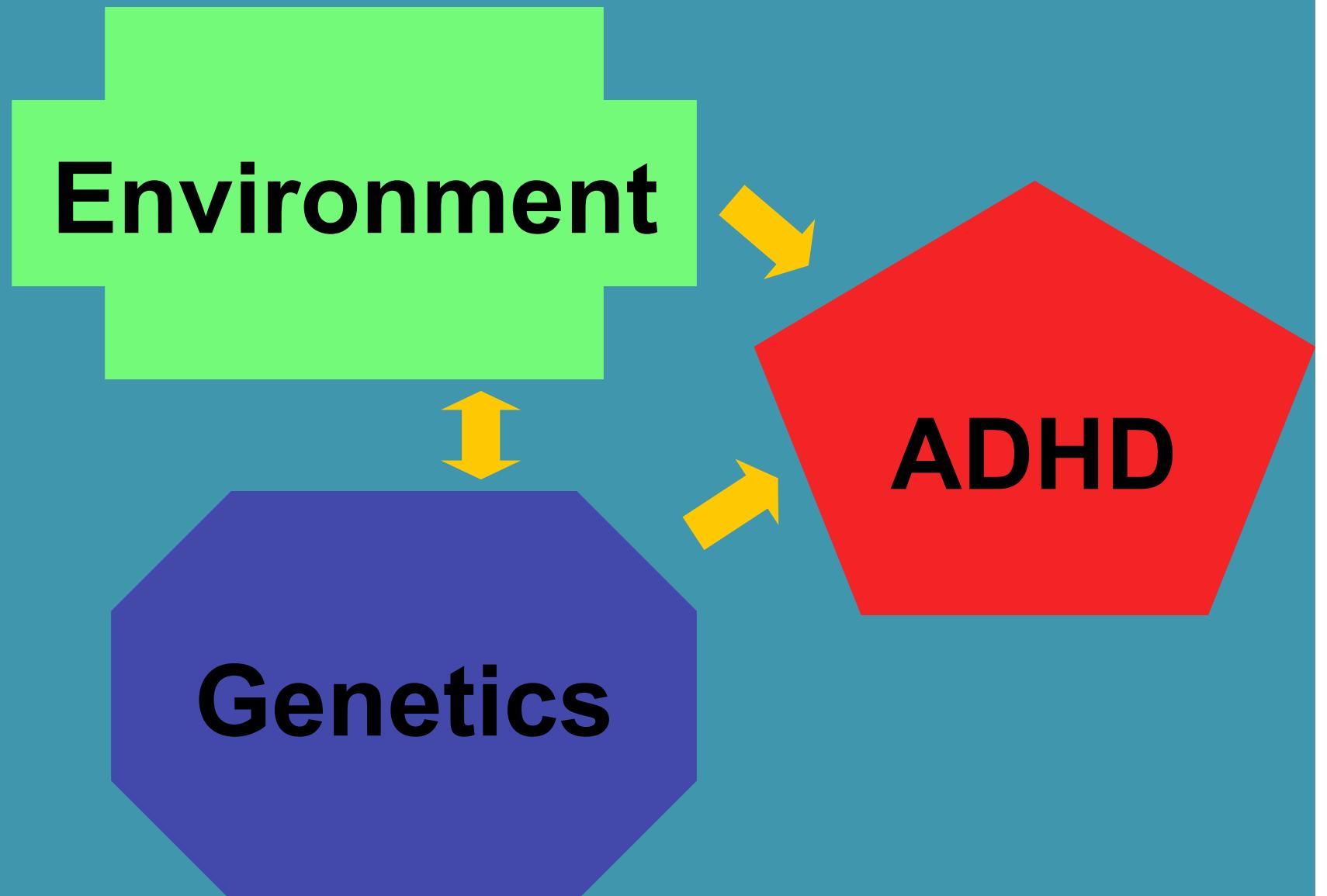
Noch ein Schritt! und plumps! der Hanns
stürzt hinab kopfüber ganz! —

Die drei Fischlein, sehr erschreckt,
haben sich sogleich versteckt.

Seht! nun steht er triefend naß!
Ei, das ist ein schlechter Spaß!
Wasser läuft dem armen Wicht
aus den Haaren ins Gesicht,
aus den Kleidern, von den Armen,
und es friert ihn zum Erbarmen.

Doch die Fischlein alle drei,
schwimmen hurtig gleich herbei;
streckens Köpflein aus der Flut,
lachen, daß man's hören tut,
lachen fort noch lange Zeit.
Und die Mappe schwimmt schon weit.

What causes ADHD?



Understanding Genetic and Environmental Influences Using Twin Studies



*Monozygotic
(MZ) Twins*

*100% genes
100% home environment*



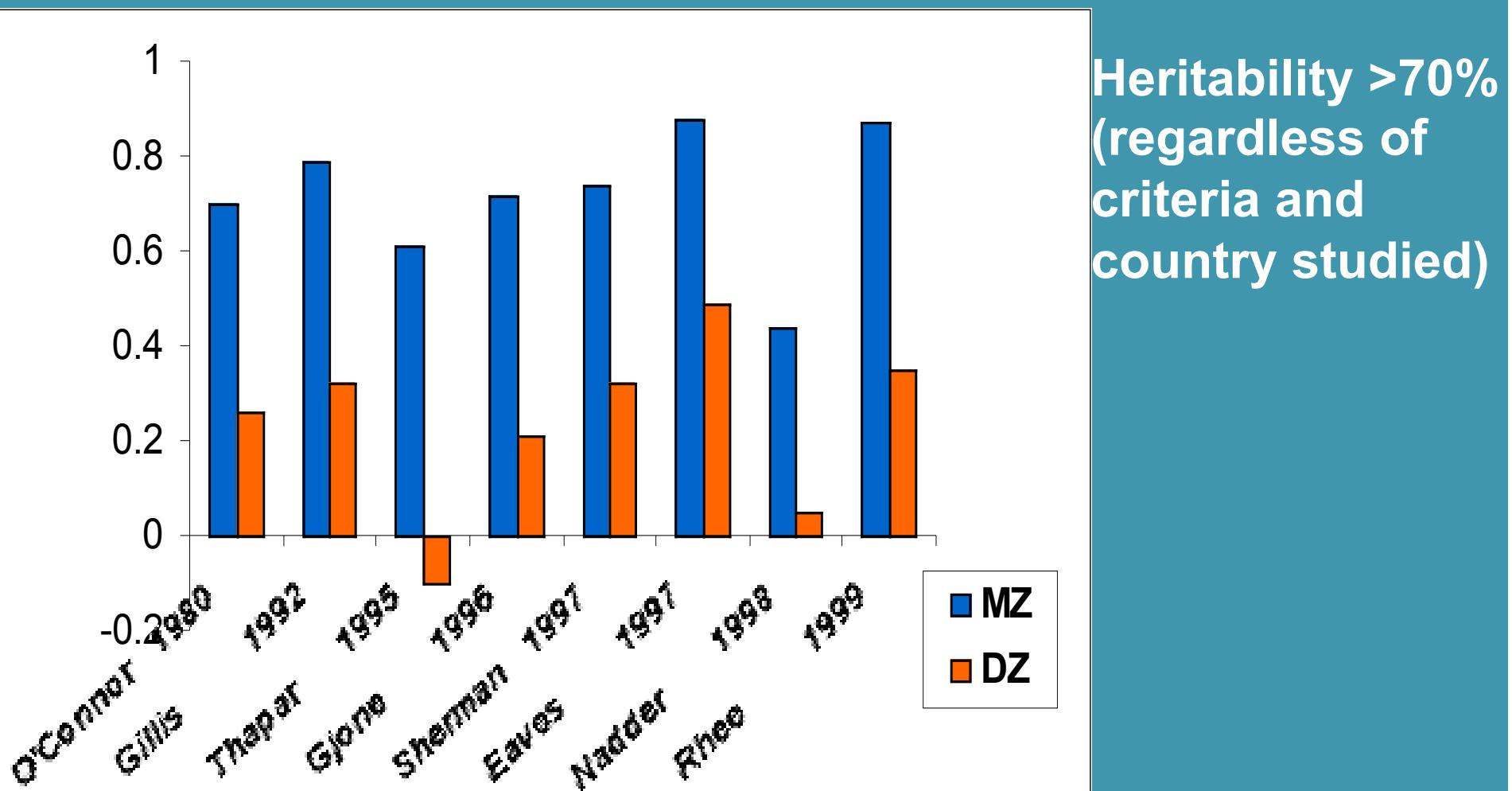
*Dizygotic
(DZ) Twins*

*50% genes
100% home environment*

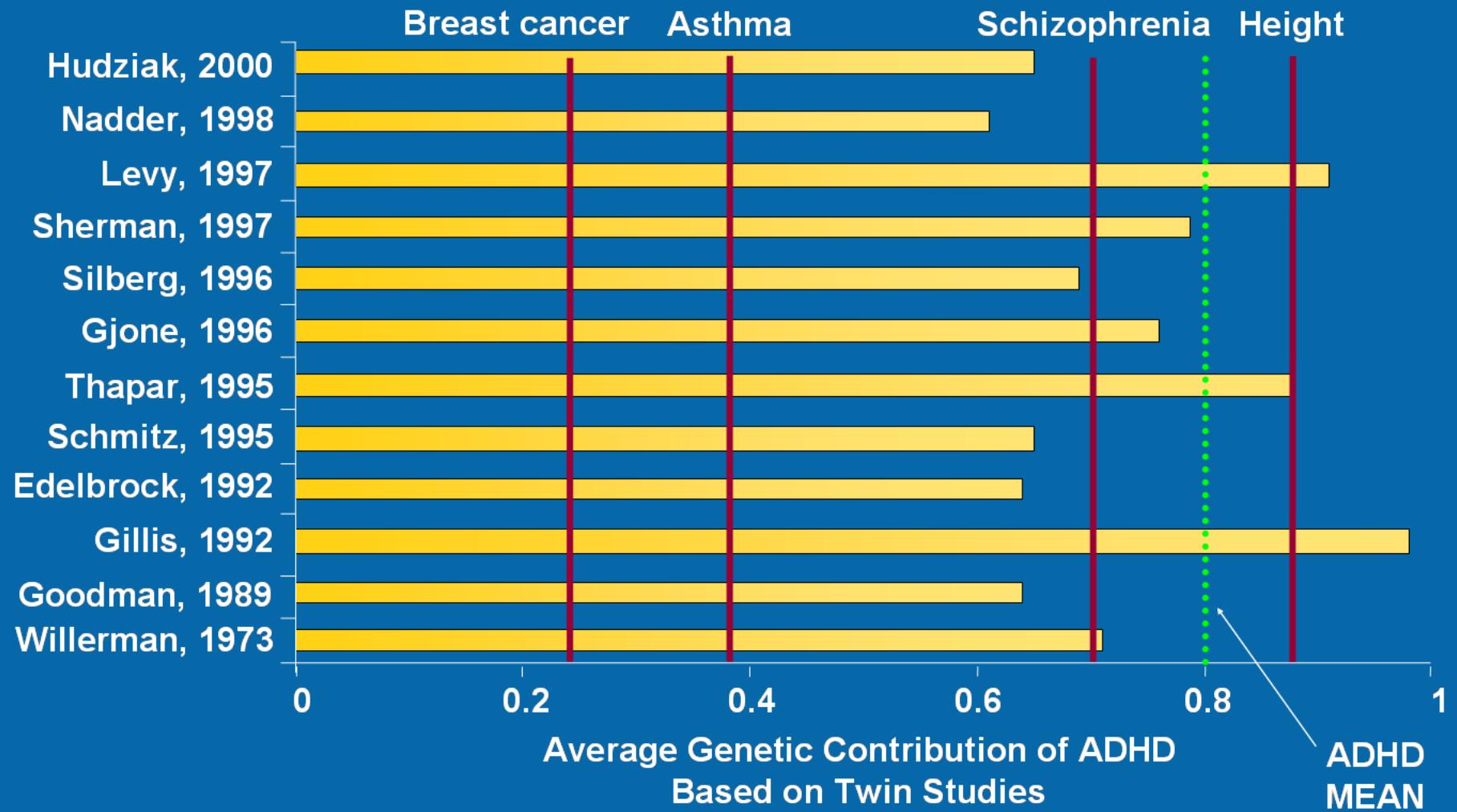
We are a combination of our genes and environment.

Genetics of ADHD

Twin concordance studies in ADHD



Studies Show ADHD Is a Genetic Disorder



Faraone SV. *J Am Acad Child Adolesc Psychiatry*. 2000;39:1455-1457. Hemminki K, Mutanen P. *Mutation Res*. 2001;473:11-21. Palmer LJ et al. *Eur Respir J*. 2001;17:696-702. Tsuang MT et al. *Br J Psychiatry*. 2001;178(suppl 40):S18-S24. Brown MW et al. *BMC Genetics* 2003. www.biomedcentral.com/1471-2156/4/s1/S32.

Name	Life prevalence	Heritability	Essential characteristics	Notable feature
Alzheimer's disease	0.132	0.58	Dementia, defining neuropathology	Of the top ten causes of death in the United States, Alzheimer's disease alone has increasing mortality
Attention-deficit hyperactivity disorder (ADHD)	0.053	0.75	Persistent inattention, hyperactivity, impulsivity	Costs estimated at $\sim \$US100 \times 10^9$ per year
Alcohol dependence (ALC)	0.178	0.57	Persistent ethanol use despite tolerance, withdrawal, dysfunction	Most expensive psychiatric disorder (total costs exceed $US\$225 \times 10^9$ per year)
Anorexia nervosa	0.006	0.56	Dangerously low weight from self-starvation	Notably high standardized mortality ratio
Autism spectrum disorder (ASD)	0.001	0.80	Markedly abnormal social interaction and communication beginning before age 3	Huge range of function, from people requiring complete daily care to exceptional occupational achievement
Bipolar disorder (BIP)	0.007	0.75	Manic-depressive illness, episodes of mania, usually with major depressive disorder	As a group, nearly as disabling as schizophrenia
Major depressive disorder (MDD)	0.130	0.37	Unipolar depression, marked and persistent dysphoria with physical and cognitive symptoms	Ranks number one in the burden of disease in the world
Nicotine dependence (NIC)	0.240	0.67	Persistent nicotine use with physical dependence (usually cigarettes)	Major preventable risk factor for many diseases
Schizophrenia (SCZ)	0.004	0.81	Long-standing delusions and hallucinations	Life expectancy decreased by 12–15 years

*Most of these definitions are made more restrictive by requiring persistence over time (for example, the criteria for SCZ require ≥ 6 months of symptoms), substantial impairment and presence across multiple different contexts. See Supplementary information S1 (table) for more detail. Additional sources are REFS 1,2,181–183).

Clinical Approaches to ADHD

Determination of phenotypic severity

ADHD subtypes

*Inattention
Hyperactivity
Impulsivity*

Comorbidities

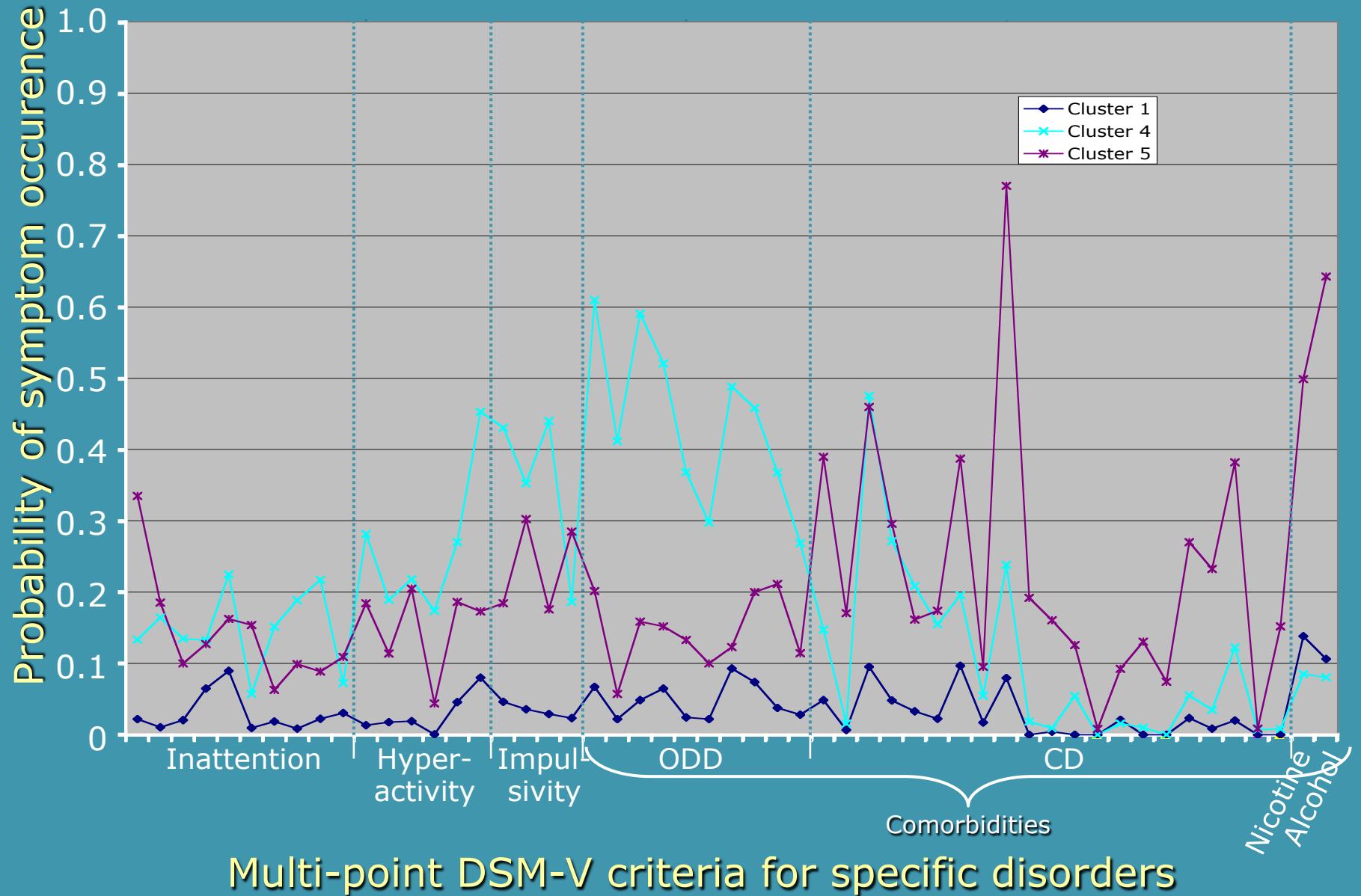
*ODD, CD
Alcohol dependence
Nicotine dependence
Depression,
Anxiety, Phobias*

Severity

*ADHD
Comorbid
Clusters*



Populations Segregate into Phenotypic Clusters

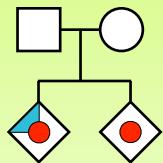


Research Designs for Human Genetic Studies

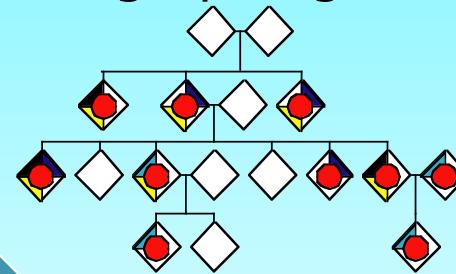
- Possible designs:
 - Determine heritability estimates
 - Candidate gene studies
 - Genome wide scans
- Types of studies:
 - Sib pairs
 - Family studies (TDT, linkage, etc)
 - Association studies (case/control)

Genetic Approaches to ADHD

Small pedigrees



Large pedigrees



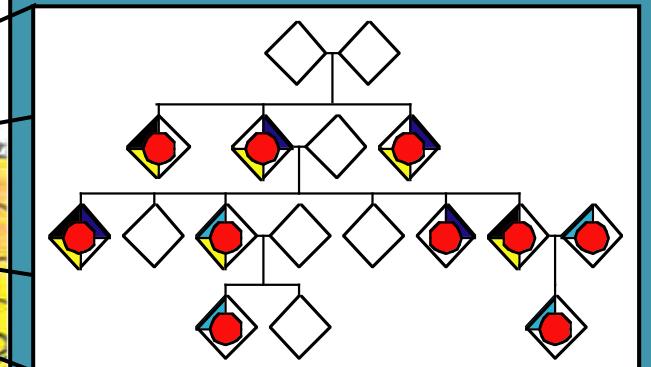
Disadvantages:
Heterogeneity
Large samples

Disadvantages:
Genetic isolate
Bi-lineality

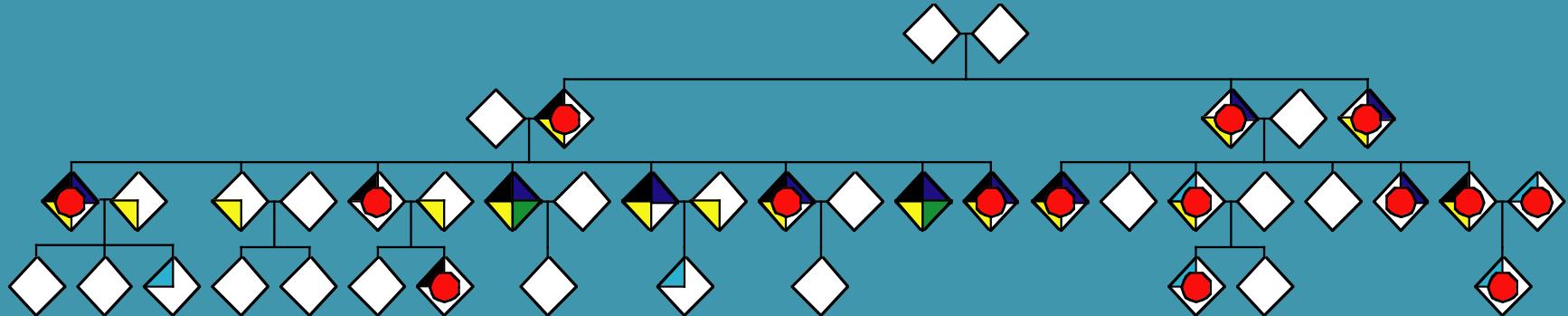
Pa

Identifying
ADHD
Genes

Genetics of Population Isolates: Paisas in Antioquia



Genetics of Population Isolates: Paisas in Antioquia



Co-morbidities

◆ ADHD

◆ CD
(Conduct disorder)

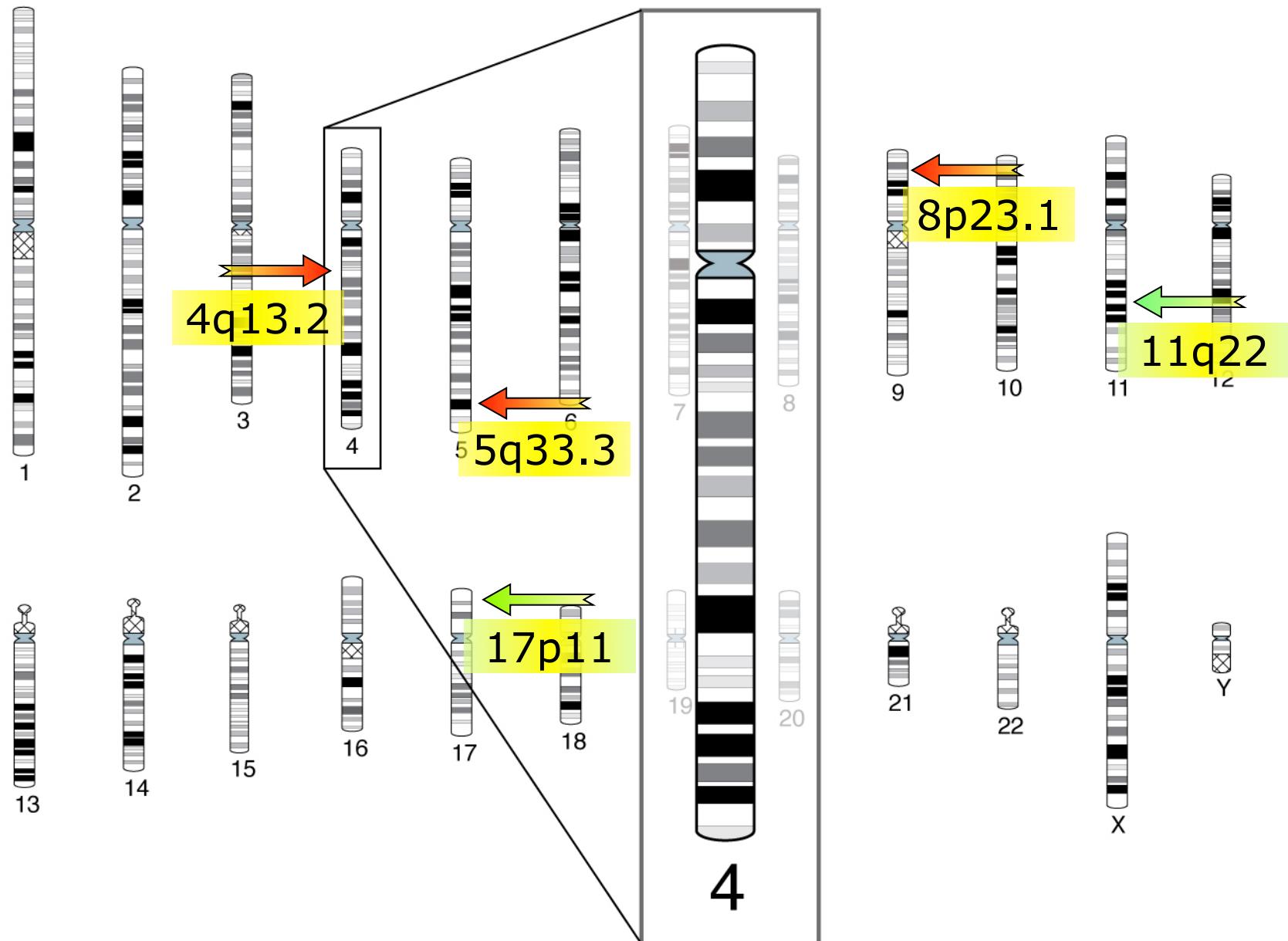
◆ Alcohol
dependence

◆ Possibly
affected

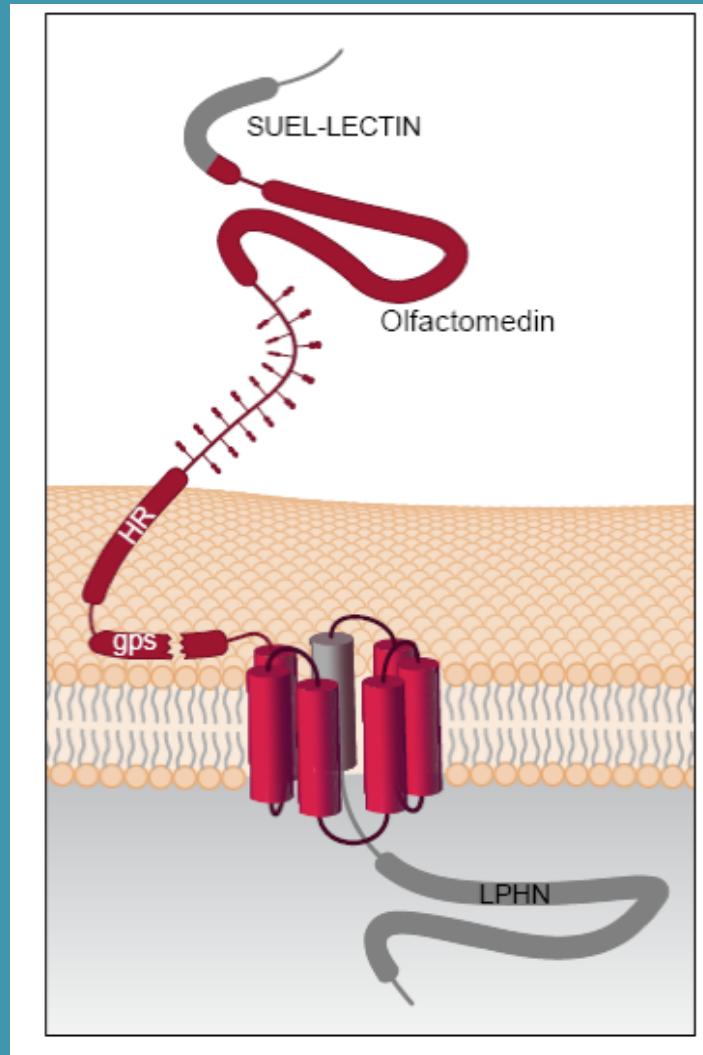
◆ ODD
(Oppositional
defiant disorder)

◆ Nicotine
dependence

Genome-Wide Scan for ADHD Linkage



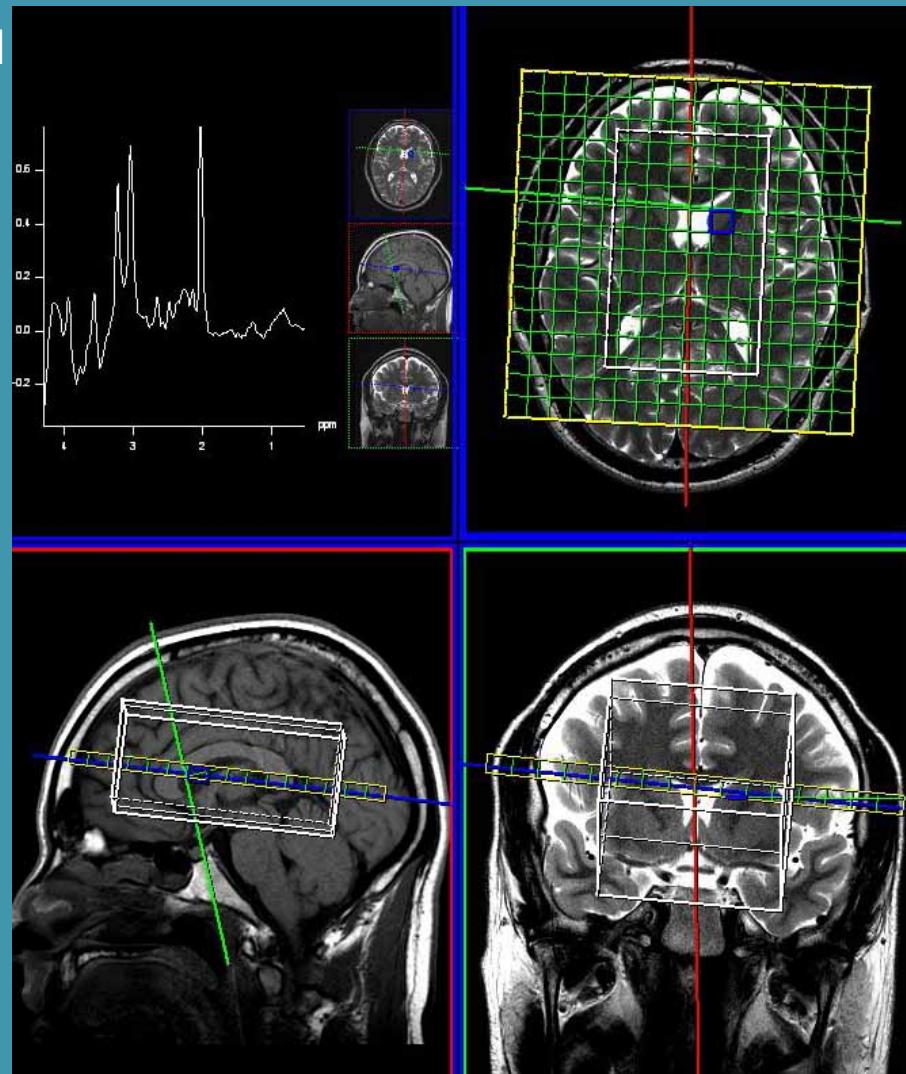
Latrophilin 3 is a member of the LPHN subfamily of G-protein coupled receptors (GPCRs)



Typical latrophilin structure

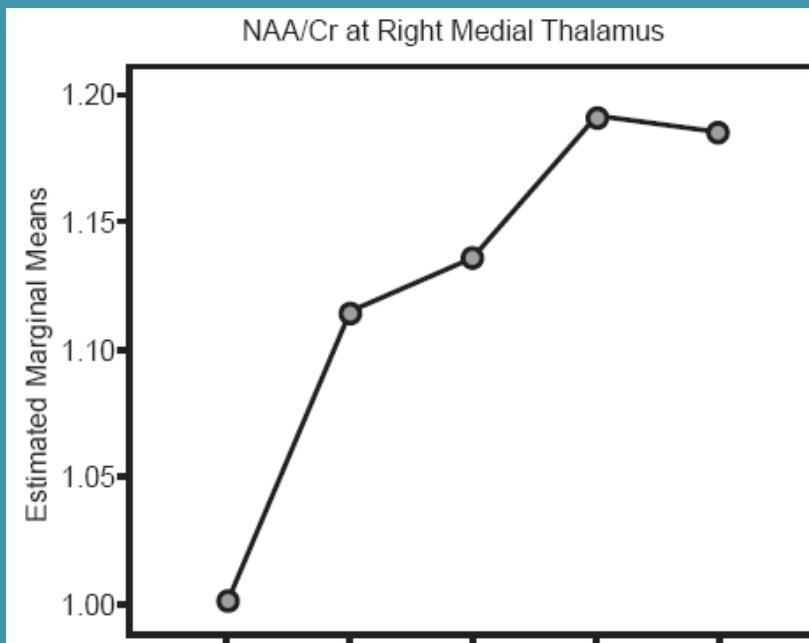
Metabolic Brain Analysis Using Proton Magnetic Resonance Spectroscopy (1H-MRS)

- 1H-MRS provides an index of neuronal number, metabolism or viability.
- N-acetylaspartate/creatinine ratio is decreased in ADHD individuals.
- We screened in the Paisas:
- 15 individuals with at least one copy of the susceptibility haplotype
- 10 individuals with at least one copy of the protective haplotype
- 8 individuals with other, different haplotype variants

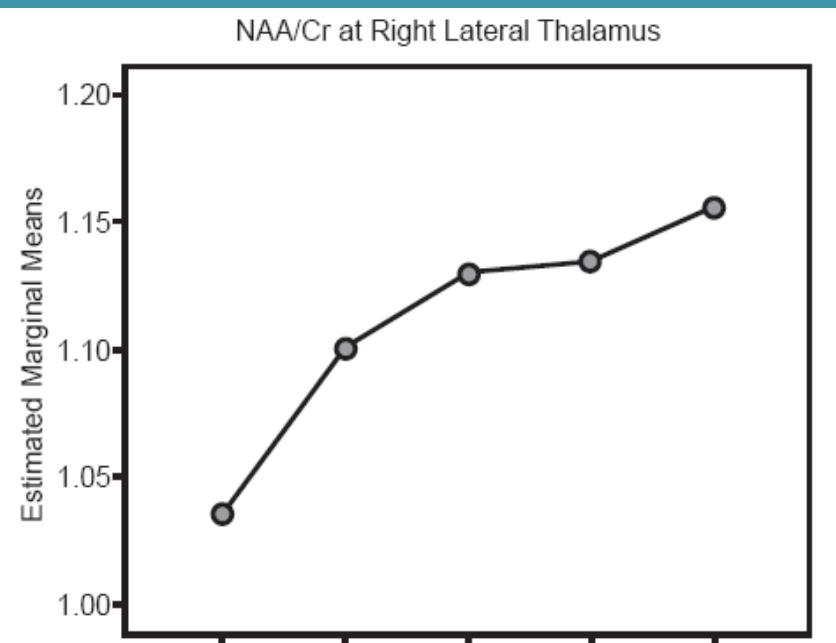


Metabolic Brain Analysis: N-acetylaspartate to Creatine ratios (NAA/Cr)

Right medial thalamus



Right lateral thalamus



2S 1S 1P 2P C

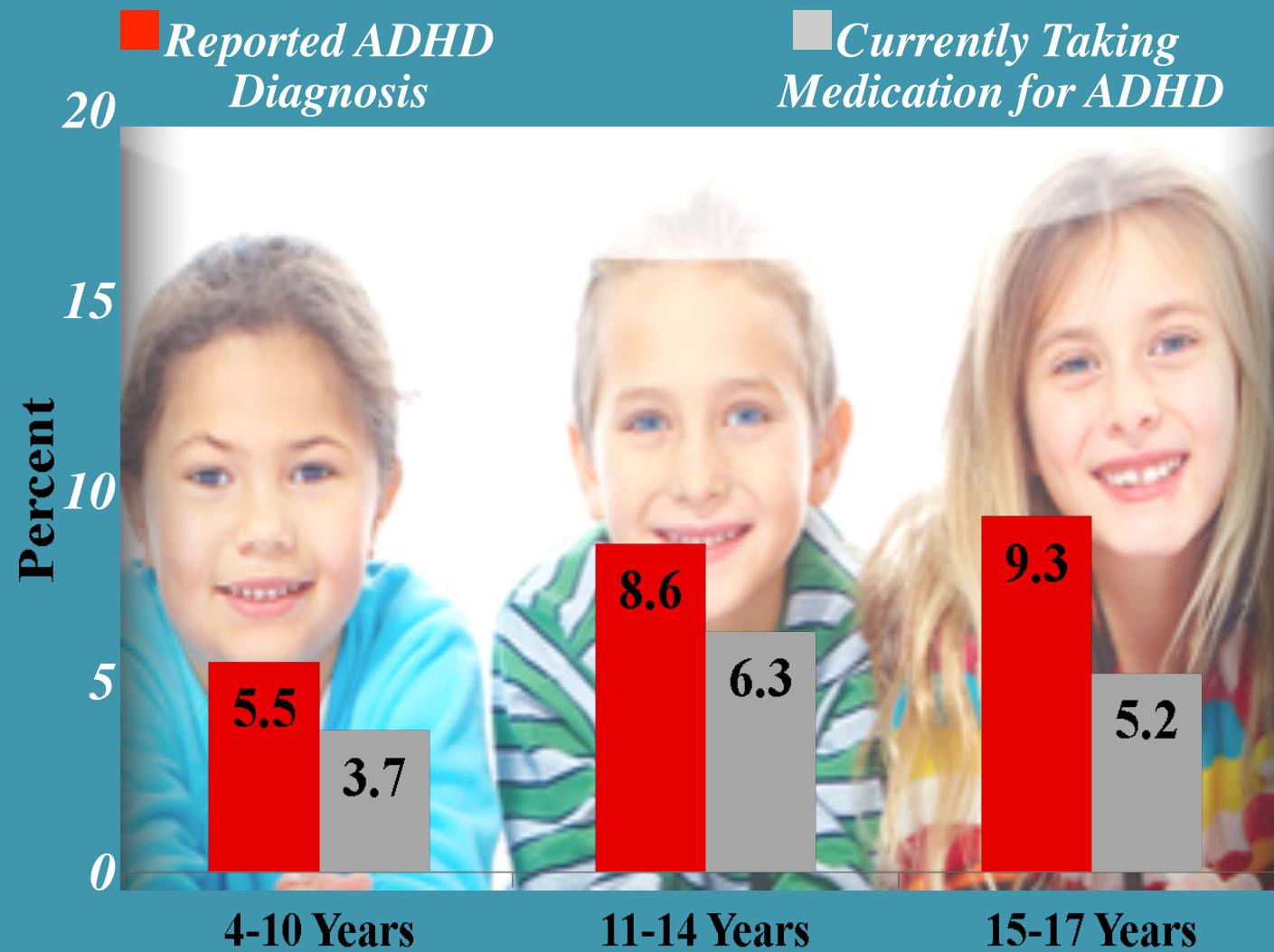
2S 1S 1P 2P C

S = susceptibility haplotype A-G-C-G,

P = protective haplotype G-G-G-A

The NAA/Cr ratio varies inversely with the number of ADHD susceptibility alleles

Prevalence of Diagnosis & Medication Treatment for ADHD Among Children Aged 4-17 Years, US, 2007

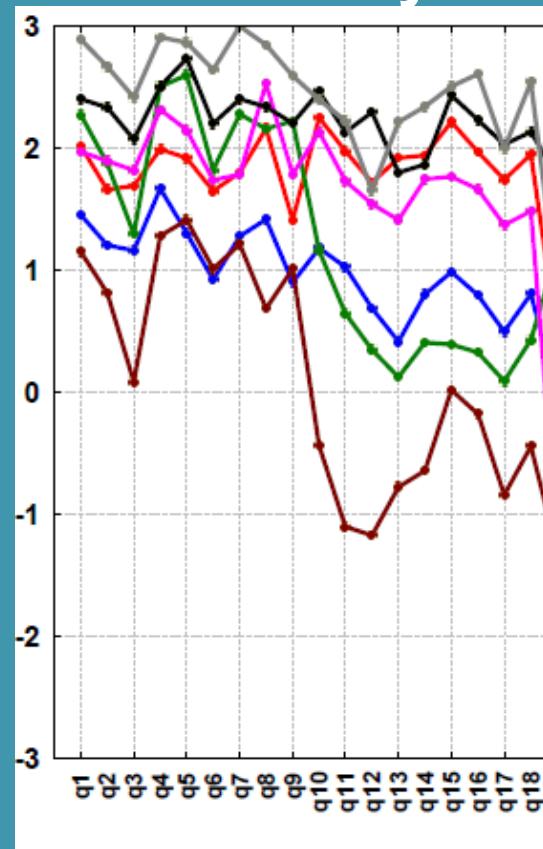


Source: CDC. MMWR 2010;59(44).

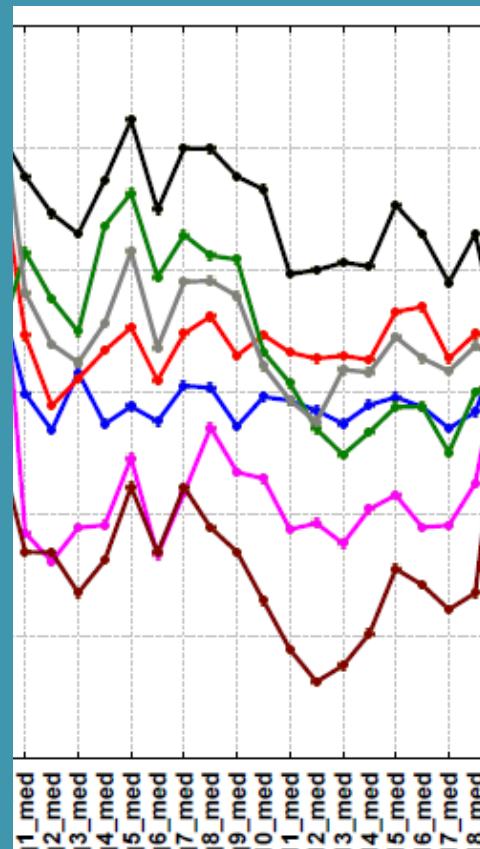
LPHN3 and ADHD: a Pharmacogenetic Study

Latent Class Analysis of Stimulant Treatment Efficacy

Symptom
Severity



Symptoms Off medication



On medication

The susceptibility allele is associated with
response to stimulant medication

Arcos-Burgos et al. 2010

Latrophilin 3 Confers Susceptibility to ADHD

- LPHN3 identified by linkage analysis
- Replication of association between LPHN3 and ADHD in worldwide samples (n=6360)
- LPHN3 is expressed in brain areas related to attention
- LPHN3 susceptibility variants alter neural circuits implicated in ADHD
- LPHN3 variants associated with response to stimulant medication

Latrophilin 3 and ADHD

Genes, Brain
and Behavior

Official publication of the International Behavioural and Neural Genetics Society

Genes, Brain and Behavior (2011) **10**: 149–157

doi: 10.1111/j.1601-183X.2010.00649.x

Contribution of *LPHN3* to the genetic susceptibility to ADHD in adulthood: a replication study

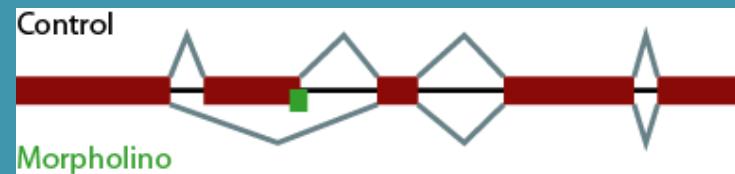
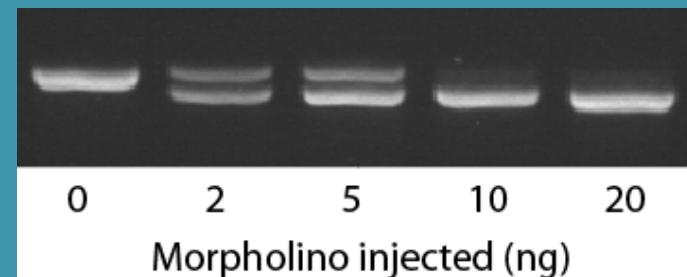
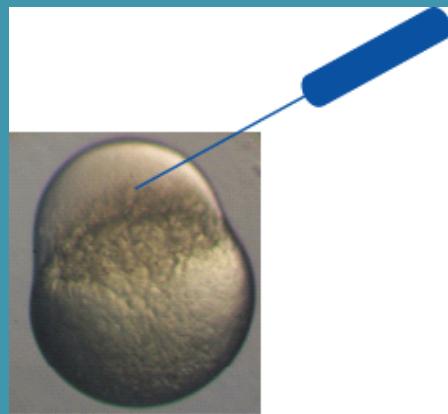
M. Ribasés*,†,‡, J. A. Ramos-Quiroga^{†,§},
C. Sánchez-Mora^{†,‡}, R. Bosch[†], V. Richarte[†],
G. Palomar[†], X. Gastaminza[†], A. Bielsa[†],
M. Arcos-Burgos[¶], M. Muenke[¶],
F. X. Castellanos^{**,**}, B. Cormand^{††,§§,¶¶},
M. Bayés*** and M. Casas^{†,§}

Keywords: Adult ADHD, attention-deficit/hyperactivity disorder, case–control association study, *LPHN3*

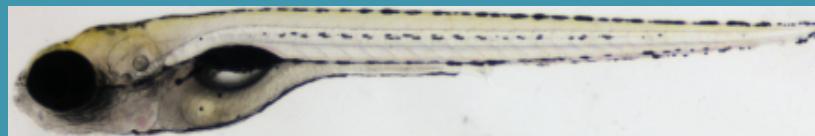
Received 22 March 2010, revised 2 July 2010 and 24 August 2010, accepted for publication 31 August 2010

Behavioral Genetics in Zebrafish

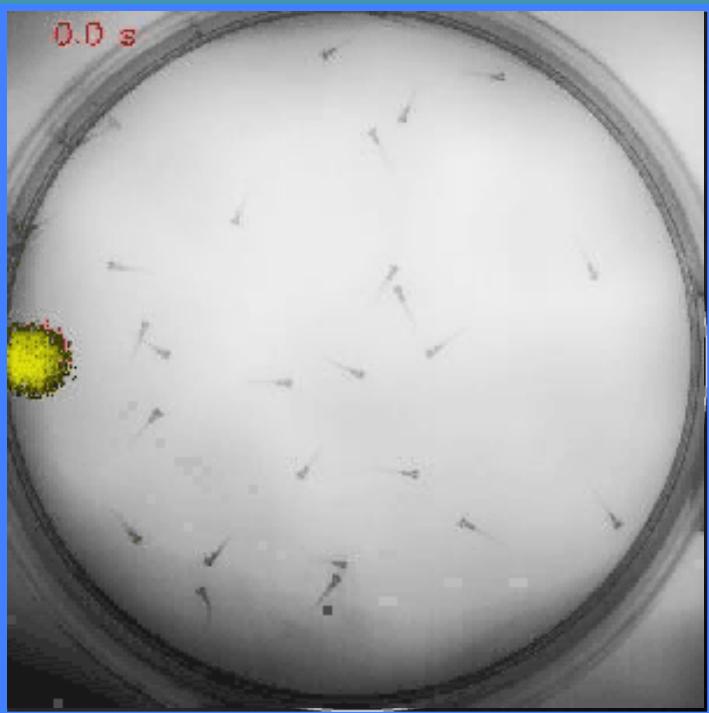
1. Inject morpholino against gene of interest into fertilized egg
2. Check splice blocking with RTPCR



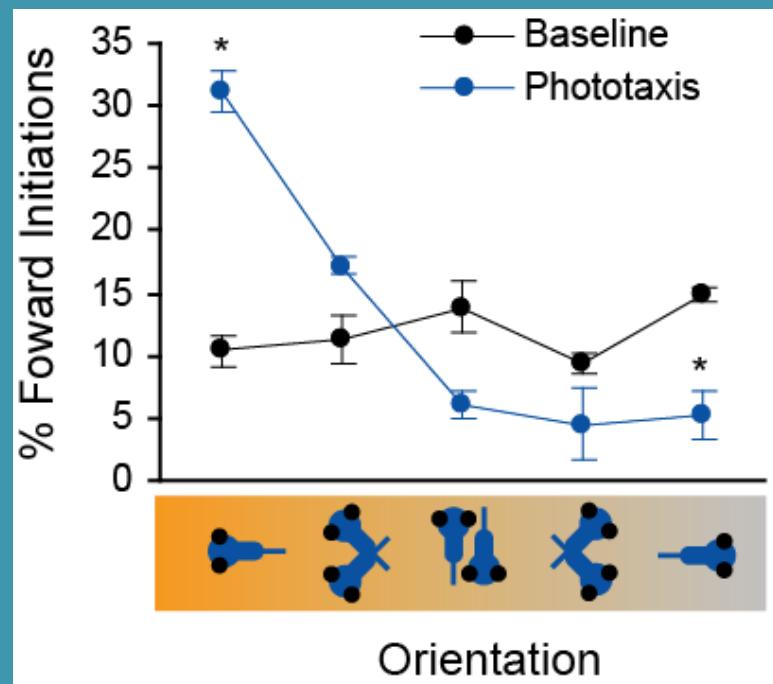
3. Raise to 5 days post fertilization when larvae are freely swimming



Phototaxis Assay for Locomotor Activity



During phototaxis, larvae rapidly approach a target light cue



Phototaxis requires selectively increasing the initiation frequency of forward movements in larvae facing the target.

LPHN3 and ADHD

Molecular Psychiatry (2012), 1–9

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www.nature.com/mp

ORIGINAL ARTICLE

The ADHD-susceptibility gene *lphn3.1* modulates dopaminergic neuron formation and locomotor activity during zebrafish development

M Lange¹, W Norton¹, M Coolen¹, M Chaminade¹, S Merker², F Proft², A Schmitt², P Vernier³, K-P Lesch² and L Bally-Cuif¹
Deeann Wallis^a, Denise S. Hill^a, Ian A. Menaez^a, Louise C. Addott^a, Rachara H. Finnell^a,
Paul J. Wellman^c, Barry Setlow^e

Epub
May 7, 2012
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Thank You

